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Safety, tolerability, and efficacy of maralixibat in adults with primary sclerosing cholangitis: Open-label pilot study

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Abstract

Background: Primary sclerosing cholangitis (PSC) is frequently associated with pruritus, which significantly impairs quality of life. Maralixibat is a selective ileal bile acid transporter (IBAT) inhibitor that lowers circulating bile acid (BA) levels and reduces pruritus in cholestatic liver diseases. This is the first proof-of-concept study of IBAT inhibition in PSC.

Methods: This open-label study evaluated the safety and tolerability of maralixibat $\leq$10 mg/d for 14 weeks in adults with PSC. Measures of pruritus, biomarkers of BA synthesis, cholestasis, and liver function were also assessed.

Abbreviations: 5-D Itch, 5-domain itch; 7αC4, 7α-hydroxy-4-cholesten-3-one; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BA, bile acid; eDiaries, electronic diaries; ET, early termination; FDA, Food and Drug Administration; HRQoL, health-related quality of life; IBAT, ileal bile acid transporter; IBD, inflammatory bowel disease; ItchRO, Itch-Reported Outcome; LDL-C, LDL-cholesterol; MOS-Sleep, Medical Outcomes Study Sleep; PBC, primary biliary cholangitis; PBC-40, primary biliary cholangitis-specific health-related quality of life questionnaire; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis; sBA, serum BA; SOC, System Organ Class; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid; TEAE, treatment-emergent adverse event; UC, ulcerative colitis; ULN, upper limit of normal.

Results: Of 27 enrolled participants, 85.2% completed treatment. Gastrointestinal treatment-emergent adverse events (TEAEs) occurred in 81.5%, with diarrhea in 51.9%. TEAEs were mostly mild or moderate (63.0%); 1 serious TEAE (cholangitis) was considered treatment related. Mean serum BA (sBA) levels decreased by 16.7% (−14.84 μmol/L; 95% CI, −27.25 to −2.43; $p = 0.0043$) by week 14/early termination (ET). In participants with baseline sBA levels above normal (n = 18), mean sBA decreased by 40.0% (−22.3 μmol/L, 95% CI, −40.38 to −4.3; $p = 0.004$) by week 14/ET. Liver enzyme elevations were not significant; however, increases of unknown clinical significance in conjugated bilirubin levels were observed. ItchRO weekly sum scores decreased from baseline to week 14/ET by 8.4% ($p = 0.0495$), by 12.6% ($p = 0.0275$) in 18 participants with pruritus at baseline, and by 70% ($p = 0.0078$) in 8 participants with ItchRO daily average score ≥ 3 at baseline.

Conclusions: Maralixibat was associated with reduced sBA levels in adults with PSC. In participants with more severe baseline pruritus, pruritus improved significantly from baseline. TEAEs were mostly gastrointestinal related. These results support further investigation of IBAT inhibitors for adults with PSC-associated pruritus. ClinicalTrials.gov: NCT02061540.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a rare, chronic, progressive cholestatic liver disease of unknown etiology.[1,2] In PSC, damage to the bile ducts impedes bile acid (BA) flow, exposing the liver to cytotoxic BAs and causing hepatocyte injury.[3] This liver damage often progresses to fibrosis, cirrhosis, and eventual liver failure.[1] Common signs and symptoms of PSC include pruritus, fatigue, jaundice, and weight loss. Elevations in serum bile acids (sBAs) and in serum alkaline phosphatase (ALP) levels, as well as fluctuations in levels of other liver enzymes, are also common.[1,2] PSC is frequently associated with inflammatory bowel disease (IBD), which may suggest an underlying immune-mediated pathology.[1] Currently, there are no medical therapies that alter the natural progression of PSC, leaving liver transplantation as the only means of treatment once end-stage liver disease is reached.

In addition to progressive liver disease, patients with PSC experience symptoms including abdominal pain and pruritus, which affects their quality of life negatively.[4] Endoscopic treatment of biliary strictures may relieve pruritus in patients with a relevant stricture,[2,5] but patients mostly rely on symptomatic treatments, such as cholestyramine, rifampicin, naltrexone, or sertraline, which are often ineffective or associated with potentially significant adverse effects.[6] Ursodeoxycholic acid, commonly used in the treatment of patients with PSC, may improve liver chemistries but does not significantly reduce pruritus.[4,6,7] Thus, there remains a significant unmet need for the symptomatic management of pruritus in patients with PSC.

The precise mechanism of pruritus associated with cholestatic liver disease, including PSC, remains poorly understood. BAs, which are critical mediators of liver injury in cholestatic liver disease and have long been proposed as a key pruritogen, are synthesized in the liver and released into the intestinal tract to facilitate digestion.[3,8,9] Approximately 95% of the BA pool is reabsorbed and transported back to the liver through the portal vein, while the remainder is excreted in the feces.[10] Intestinal reabsorption of BAs occurs in the terminal ileum through the ileal bile acid transporter (IBAT).[11] Maralixibat chloride (formerly SHP625 and LUM001) is a potent, selective, and minimally absorbed inhibitor of IBAT.[12–14] Interruption of BA recirculation with an IBAT inhibitor reduces intestinal BA reabsorption and increases mean fecal BA excretion up to 8-fold.[11] Treatment with IBAT inhibitors, including maralixibat (the first US Food and Drug Administration [FDA]-approved treatment of cholestatic pruritus in patients with ALGS who are 3 months of age and older),[15] have demonstrated reduction in pruritus and sBA, without deterioration of liver function in patients with cholestatic liver disease (Alagille syndrome, primary biliary cholangitis [PBC], or progressive familial intrahepatic cholestasis [PFIC]).[8,16–21] In addition to BAs, studies have indicated that autotaxin (a marker of severity of liver injury and transplant-free survival), 7α-hydroxy-4-cholesten-3-one (7αC4) (a marker of *de novo*

BA synthesis), and FGF-19 (a marker of bile salt synthesis) are putative biomarkers of cholestatic liver disease.[22–27] Here, we report the results of the first open-label, pilot study to investigate the safety, tolerability, and efficacy of maralixibat in adults with PSC.

METHODS

Ethics and conduct

This open-label, phase 2, safety, tolerability, and efficacy study of maralixibat in adults with PSC was conducted between March 2014 and February 2016 at 8 centers in the US, UK, and Canada (CAMEO study; ClinicalTrials.gov identifier: NCT02061540). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, the 2018 edition of the Declaration of Istanbul, and was approved by institutional review boards or ethic committees from each study site and was approved by an independent ethics committee. It was conducted in accordance with the International Conference on Harmonization of Good Clinical Practice guidelines, as well as all applicable federal, local, ethical, and legal requirements. All participants provided written informed consent before commencing any study procedures.

Study design

After screening and a 4-week observation period, eligible participants received maralixibat at doses of up to 10 mg/d for 14 weeks. Maralixibat tablets were taken orally, at least 30 minutes before breakfast each day. The 14-week treatment period comprised a 6-week dose-escalation phase and an 8-week stable-dosing phase. During dose escalation, maralixibat dose was increased at weekly intervals (week 1, 0.5 mg/d; week 2, 1 mg/d; week 3, 2.5 mg/d; week 4, 5 mg/d; week 5, 7.5 mg/d; and week 6, 10 mg/d). Dose escalation aimed to reduce the risk of dose-limiting gastrointestinal adverse events (AEs) that have been associated with IBAT inhibition. During stable dosing (weeks 7–14), participants received up to 10 mg/d. The maximum maralixibat dose of 10 mg/d was selected based on previous studies in healthy volunteers and individuals with hypercholesterolemia and was lower than that assessed in previous studies in other cholestatic liver diseases to avoid unnecessary aggravation of IBD in patients with PSC.

Discontinuation criteria

Further clinical investigation was prompted if, at any time during the study, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels were more than 5-fold higher than at baseline in a participant with ALT or AST levels at or below the upper limit of normal (ULN) at baseline or more than 3-fold higher than baseline in a participant with ALT or AST levels above the ULN at baseline. Further clinical investigation was also prompted if ALT or AST levels were more than 3-fold above the ULN and total bilirubin was more than 2-fold above the ULN. Maralixibat treatment was suspended if ALT or AST levels were10-fold higher than the ULN; if ALT or AST levels were 3-fold higher than the ULN and total bilirubin was more than 2-fold above the ULN (or an international normalized ratio of >1.5 without an alternative explanation); if ALT or AST levels were 3-fold higher than the ULN with the appearance of signs and symptoms consistent with a drug reaction or bacterial cholangitis; or if ALP were 2-fold higher than at baseline.

Participants

Participants were aged 18–80 years with a diagnosis of PSC according to the American Association for the Study of Liver Diseases criteria.[28] In addition, participants had to have a Mayo Ulcerative Colitis disease activity score of 2 or below and, if receiving azathioprine, no IBD flares within 6 months of screening. Key exclusion criteria were small duct PSC, the presence of a dominant stricture (unless brushings and/or biopsies were negative for dysplasia or malignancy within 6 months of screening), biliary tree interventions for the treatment of clinically significant strictures within 6 months of screening, IBD flare (Mayo Ulcerative Colitis disease activity score >5) within 3 months of screening, secondary cause of sclerosing cholangitis, ALT or AST greater than or equal to 5-fold above the ULN at screening, advanced clinical complications of PSC, clinically significant hepatic decompensation, or a history or presence of concomitant liver disease. Participants with any Itch-Reported Outcome (ItchRO) score or ALP level were included. Participants were also excluded if they received rituximab within 12 months before treatment; hydroxychloroquine, methotrexate, oral vancomycin, colchicine, bezafibrate/fenofibrate, anti-TNF therapies, leflunomide, tocilizumab, or ≥ 10 mg prednisone within 6 months before treatment; and ursodeoxycholic acid and BA resins within 28 days before treatment.

Outcome measures

The primary objective was to evaluate the safety and tolerability of maralixibat at doses up to 10 mg/d over 14 weeks. Safety and tolerability outcomes comprised treatment-emergent adverse events (TEAEs), gastrointestinal signs and symptoms, concomitant medications, clinical

laboratory results, and physical examinations. TEAEs of special interest were analyzed in 2 categories: gastrointestinal events and events related to liver deterioration (including some gastrointestinal events). Treatment exposure and compliance were calculated based on the dose and number of tablets taken as recorded by participants in electronic diaries (eDiaries). Gastrointestinal signs and symptoms were self-reported daily in eDiaries using a 3-item questionnaire (0–3 points per item); higher scores indicated worsening of abdominal pain/discomfort, more liquid stools, and more rectal bleeding.

The primary efficacy measure was change from baseline to week 14 or early termination (ET) in sBA level after a 12-hour fast. Changes in sBA at weeks 6 and 14 were exploratory outcomes. Secondary efficacy measures were changes from baseline to week 14/ET in liver biomarkers (ALT, AST, ALP, and total and conjugated bilirubin) and self-reported pruritus (ItchRO weekly sum scores). Changes in these parameters at weeks 3, 6, and 14 were exploratory outcomes. Participants completed Adult ItchRO eDiaries twice daily (morning and evening), rating itch severity from 0 (none) to 10 (most severe). The higher of the 2 daily scores was used to calculate weekly sum and daily average scores.

Additional exploratory measures included changes from baseline to week 14/ET in other measures of pruritus [adult ItchRO average daily scores, 5-domain Itch (5-D Itch),[29] Patient Impression of Change, and Patient Global Therapeutic Benefit], health-related quality of life (HRQoL) (primary biliary cholangitis-specific HRQoL questionnaire [PBC-40])[30,31], sleep [Medical Outcomes Study Sleep (MOS-Sleep)].[32] and biomarkers of BA synthesis and cholestasis [serum 7αC4, FGF-19, FGF-21, autotaxin, total cholesterol, and LDL-cholesterol (LDL-C)]. Considering available data collected in the study, Mayo risk scores were calculated for each participant to help assess overall severity of PSC at study entry based on the following formula: $R = 0.03 \times \text{age(years)} + 0.54 \times \log[\text{bilirubin (mg/dL)}] + 0.54 \times \log[\text{AST (U/L)}] + 1.24 \times [\text{variceal bleeding (0/1)}] - 0.84 \times [\text{albumin (g/dL)}]$.[33]

A fully validated liquid chromatography-electrospray ionization-mass spectrometry proprietary assay was used to determine the sBA levels and levels of BA subspecies (glycocholic acid, taurocholic acid [TCA], taurodeoxycholic acid, and glycodeoxycholic acid), by stable-isotope dilution analysis, at a single site (Cincinnati Children's Hospital Medical Center, Cincinnati, OH). Quality control samples were prepared in human plasma or serum, stored with study samples, and assayed with each batch of study samples against freshly prepared calibration standards. Assays were validated and conducted in accordance with the Food and Drug Administration Guidance for Industry: Bioanalytical Method Validation (CDER 2001).

Outcomes were assessed during both the lead-in observation period (4 wk before the treatment period) and the treatment period (weeks 0, 3, 6, and 14/ET). Participants were also followed up by telephone at weeks 1, 2, 4, 5, and 10, and at 4 weeks after stopping treatment.

Statistical analysis

All participants who received any dose of maralixibat were included in the safety population. Efficacy outcomes were assessed in the modified intent-to-treat population, which included all participants treated with maralixibat who had a postbaseline sBA assessment. The planned population size (n = 20) was based on the practicality of recruiting participants with PSC rather than on statistical considerations.

For continuous efficacy measures, changes from baseline in fasting sBA levels, as well as ALT, AST, ALP, total bilirubin, conjugated bilirubin, and pruritus, were visually inspected for normality using a quantile–quantile plot and analyzed with a paired *t* test or paired Wilcoxon signed-rank test as appropriate. For sensitivity analyses, changes were also evaluated by analysis of covariance using a mixed linear model with baseline value as covariate. No adjustments were made for multiplicity. *p*-values from all secondary efficacy analyses are nominal.

RESULTS

Participant disposition and baseline characteristics

The modified intent-to-treat and safety populations included all 27 enrolled participants. Most participants were White (85.2%), and 66.7% were men (Table 1). Median age was 44.0 years (interquartile range: 33.0–49.0), and median time since diagnosis of PSC was 78.6 months (interquartile range: 36.4–130.4). Itch was reported by 81.5% (n = 22) at baseline, and 59.3% (n = 16) reported having used medication to treat their itch in the past, while 48.1% (n = 13) had previously used ursodeoxycholic acid for the treatment of their pruritus. The mean (SD) Mayo risk score for the modified intent-to-treat population (n = 27) was 0.09 (0.882), indicative of a population with an excellent prognosis for long-term survival and relatively non-advanced disease.

Of the 27 participants, 23 (85.2%) completed the 14-week treatment with maralixibat. None of the participants discontinued due to prespecified changes in liver biochemistry. Two participants discontinued due to TEAEs of moderate abdominal discomfort and severe fatigue (n = 1 each), and 2 withdrew consent. Five participants (18.5%) required down titration, predominantly due to gastrointestinal events. Of these 5 participants with gastrointestinal events, 3 had grade 1 severity [1 participant with a history of ulcerative

TABLE 1 Participant demographics and disease characteristics at baseline

Characteristic	Overall population (N = 27)
Age, years (SD)	43.7 (11.4)
Male	18 (66.7)
Body mass index, kg/m^2 (SD)	26.2 (4.0)
Race	
White	23 (85.2)
More than 1 race	2 (7.4)
Black or African American	1 (3.7)
Asian	1 (3.7)
Country	
USA	14 (51.9)
Canada	9 (33.3)
UK	4 (14.8)
Time since diagnosis, months (SD)	94.0 (75.4)
Mayo risk score, mean (SD)	0.09 (0.882)
Symptoms of PSC	
Itching	22 (81.5)
UC	15 (55.6)
Fatigue	13 (48.1)
Inflammatory bowel disease	12 (44.4)
Other symptom(s)	2 (7.4)
Used medication for itching in the past	16 (59.3)
Concomitant medications used by ≥15% of participants	
Antidiarrheals, intestinal anti-inflammatories, anti-infectives	14 (51.9)
Analgesics	10 (37.0)
Vitamins	9 (33.3)
Psychoanaleptics	8 (29.6)
Antibacterials for systemic use	7 (25.9)
Beta-blockers	7 (25.9)
Drugs for acid-related disorders	7 (25.9)
Lipid-modifying agents	6 (22.2)
Psycholeptics	6 (22.2)
Oral therapies used by participants before treat pruritus	
Ursodeoxycholic acid	13 (48.1)
Binding resins (eg, cholestyramine, colestipol, and colesevelam)	8 (29.6)

Note: All values are n (%) unless otherwise specified.
Abbreviations: IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

colitis (UC)], 1 had grade 2 severity (history of UC), and another had separate gastrointestinal events of grade 1 and 3 severities (no history of IBD). The mean (SD) dose of maralixibat at the beginning of the stable-dosing period (or the last dose received in participants who discontinued during the dose-escalation period) was 6.56 mg/d (2.02), and treatment compliance was 98.7%.

TABLE 2 Treatment-emergent adverse events

TEAEs reported in ≥ 5% of participants	Safety population (N = 27), n (%)
TEAEs	25 (92.6)
Gastrointestinal disorders	
Diarrhea	14 (51.9)
Nausea	9 (33.3)
Abdominal pain	8 (29.6)
Abdominal distension	4 (14.8)
Abdominal discomfort	3 (11.1)
Abdominal pain upper	2 (7.4)
Frequent bowel movements	2 (7.4)
General disorders and administration-site conditions	
Fatigue	4 (14.8)
Pyrexia	2 (7.4)
Asthenia	2 (7.4)
Hepatobiliary disorders[a]	
Cholangitis	2 (7.4)
Hepatomegaly	2 (7.4)
Infections and infestations	
Nasopharyngitis	2 (7.4)
Musculoskeletal and connective tissue disorders	
Arthralgia	3 (11.1)
Neck pain	2 (7.4)
Muscle spasms	2 (7.4)
Nervous system disorder	
Headache	6 (22.2)
AEs of special interest	
TEAEs of special interest (gastrointestinal)[b]	21 (77.8)
TEAEs of special interest (liver dysfunction)	22 (81.5)
Gastrointestinal disorders[a]	22 (81.5)
Hepatobiliary disorders[c]	4 (14.8)
Decreased appetite	1 (3.7)
Pruritus	1 (3.7)

[a]TEAEs associated with liver deterioration (the definition of which included the GI disorder SOC), were all the gastrointestinal and hepatobiliary disorder AEs listed in this table, plus abdominal tenderness, ascites, constipation, dyspepsia, fecal incontinence, fecaloma, gastritis, melena, upper gastrointestinal hemorrhage, defecation urgency, hemorrhoids, rectal hemorrhage, and jaundice (n = 1 each).
[b]Gastrointestinal TEAEs of special interest were all the gastrointestinal TEAEs in the table, plus abdominal tenderness, fecal incontinence, fecaloma, gastritis, and defecation urgency (n = 1 each).
[c]Hepatobiliary disorders included cholangitis, hepatomegaly (n = 2 each), and jaundice (n = 1).
Abbreviations: AE, adverse event; SOC, System Organ Class; TEAE, treatment-emergent adverse event.

Safety and tolerability

TEAEs were reported in 92.6% of participants and were mainly mild (40.7%) or moderate (22.2%) in severity. The most common TEAEs were gastrointestinal events (affecting 81.5%), including diarrhea, nausea, and

abdominal pain, reported in 51.9%, 33.3%, and 29.6% of participants, respectively (Table 2). Diarrhea occurred more frequently in participants with UC/IBD (55.6%) compared with those without UC/IBD (44.4%). However, nausea and abdominal pain occurred at a lower rate in participants with UC/IBD (22.2% and 22.2% for each) versus those without UC/IBD (55.6% and 44.4% for each). The proportion of participants who experienced gastrointestinal TEAEs during the stable-dosing phase (46.2%) was lower than in the dose-escalation period (70.4%). Gastrointestinal AEs of special interest were reported in 77.8% of participants. Four participants (14.8%) had a total of 5 serious AEs (cholangitis, melena, upper gastrointestinal hemorrhage, appendicitis, and joint dislocation). The patient with the cholangitis AE had a history of intermittent cholangitis, and the investigators attributed the AE as possibly related to maralixibat as well as the participant's underlying PSC. All 4 participants were recovering or had recovered without discontinuation at the end of the treatment period, and only the cholangitis was considered to be related to treatment.

Mean (SD) gastrointestinal sign and symptom scores increased modestly from baseline to week 14/ET by 0.18 (0.57) for abdominal pain/discomfort, 0.31 (0.48) for liquid stools, and 0.06 (0.16) for rectal bleeding.

Efficacy

Itching and other patient-reported outcomes

Mean ItchRO weekly sum scores for all participants decreased significantly by 8.4% from baseline to week 14/ET ($p = 0.0495$), with a mean decrease of 7.67 points (95% CI, −14.13 to −1.22) in weekly sum score, from a mean of 15.0 (95% CI, 7.59–22.4) at baseline (Figure 1A). Mean ItchRO scores decreased continuously throughout the study (Figure 1B). From baseline to week 14/ET, ItchRO daily average scores did not worsen by more than 1 point in any participant but improved by more than 1 point in 8 (29.6%) participants and improved by 3 points in 6 (22.2%) participants. The 8 participants with an improvement of more than 1 point had daily average scores of 3 or above at baseline, and there was a significant mean decrease of 70% ($p = 0.0078$) in weekly sum scores from baseline to week 14/ET in this post hoc subgroup (Figure 1A). In another post hoc subgroup analysis including the 18 participants with any itching at baseline (ItchRO average daily score > 0), ItchRO weekly sum score significantly decreased by 12.6% ($p = 0.0275$) from baseline to week 14/ET (Figure 1A). Similar results were observed with the 5-D Itch scores. With any itching at baseline (ItchRO average daily score > 0), the 5-D weekly sum score significantly decreased by 30.2% ($p = 0.0004$) from baseline to week 14/ET (Figure 1C). Mean 5-D scores decreased continuously throughout the study (Figure 1D).

In the overall population (N = 27), 5-D Itch scores decreased by 22.1% from baseline to week 14/ET ($p < 0.0001$), with a mean change of −3.8 points (95% CI, −5.9 to −1.7) from a mean of 11.8 (95% CI, 9.7–13.9) at baseline. On the Patient Impression of Change scale, 14 of the 26 participants with data (53.8%) reported improved itching (much better, better, or a little better), and only 1 of 26 (3.8%) reported worsening (a little worse), with the remainder reporting no change. On the Patient Global Therapeutic Benefit instrument, treatment benefits outweighed adverse effects in 69.2% of participants, but the reverse was true in 15.4%, with the remainder reporting equivalence. Changes in mean PBC-40 fatigue domain scores and MOS-Sleep disturbance scores from baseline were not significant (Table 3).

BA composition

For the enrolled 27 participants, baseline sBA levels were correlated with baseline ItchRO scores and decreased during treatment (Table 4 and Figure 2). Between baseline and week 14/ET, mean (SD) total sBA levels decreased from 38.94 (38.66) to 24.10 (32.59) μmol/L overall. In participants whose sBA levels were elevated above the normal range (0–10 μmol/L) at baseline (n = 18), sBA levels decreased from 55.58 (37.47) to 33.24 (36.78) μmol/L by week 14/ET ($p = 0.004$). Participants with a baseline ItchRO score ≥ 3 (n = 8) generally presented with higher levels of sBA at baseline, which decreased from 73.13 (36.02) to 41.07 (46.39) μmol/L by week 14/ET ($p = 0.0781$).

Between baseline and week 14/ET, mean (SD) glycocholic acid levels decreased from 10.24 (11.94) to 6.01 (10.57) μmol/L ($p = 0.0396$) overall and from 14.73 (12.39) to 8.58 (12.23) μmol/L ($p = 0.0447$) in participants with elevated baseline sBA levels. Between baseline and week 14/ET, mean TCA levels decreased from 8.40 (10.44) to 3.13 (6.64) μmol/L ($p = 0.0009$) overall, from 12.19 (10.99) to 4.59 (7.78) μmol/L ($p = 0.0009$) in participants with elevated baseline sBA levels, and from 15.55 (7.05) to 4.57 (5.82) μmol/L ($p = 0.0116$) in participants with a baseline ItchRO score ≥ 3.

Biomarkers

Mean sBA levels decreased by 16.7% from baseline (38.9 μmol/L; 95% CI, 23.6–54.2) to week 14/ET (24.1 μmol/L; 95% CI, 11.2–37) (Table 5). Importantly, autotaxin levels decreased by 12.0% ($p = 0.0088$), including a decrease by 17.2% ($p = 0.0046$) in participants with a baseline ItchRO score of <3 (n = 18) and by 40.6% ($p = 0.0078$) in participants with an ItchRO score of ≥ 3 (n = 8). Not

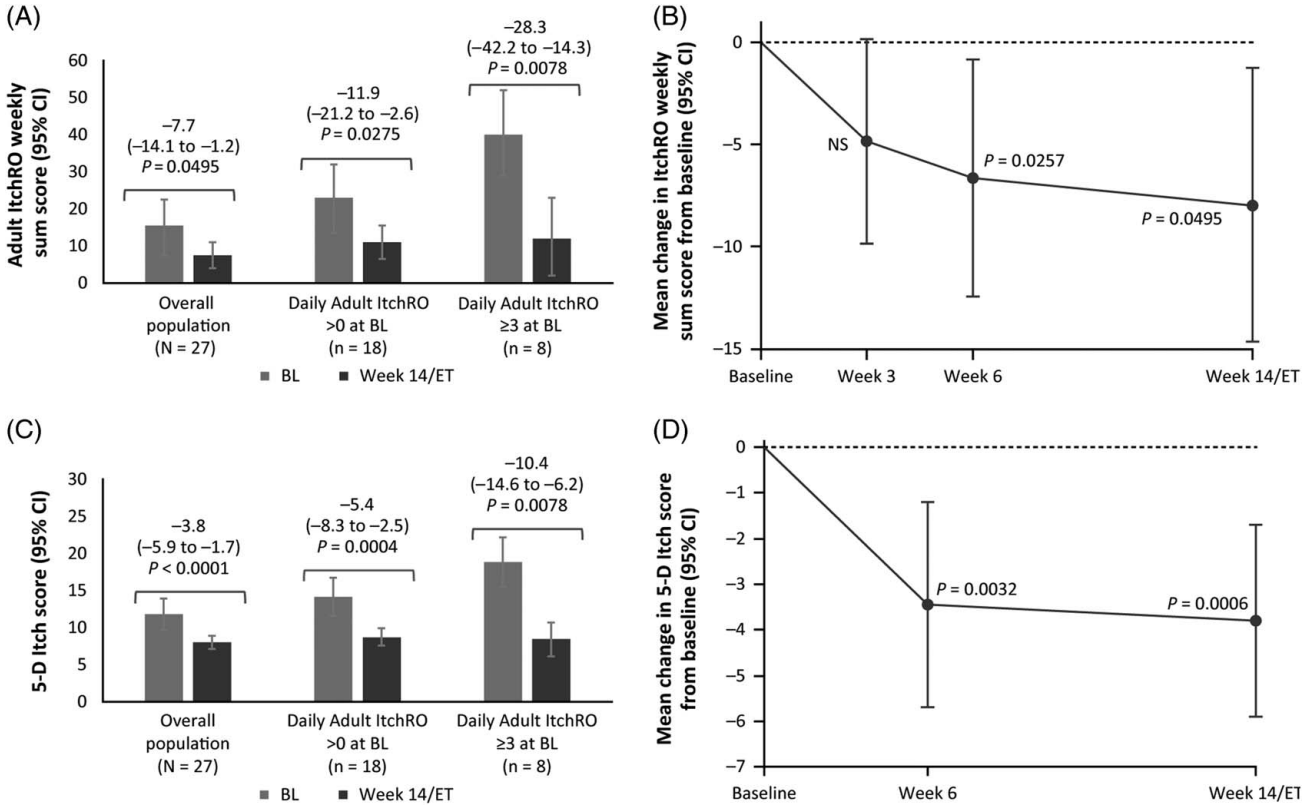

FIGURE 1 Pruritus outcomes. (A) Mean change in ItchRO weekly sum score from baseline to week 14/ET in the modified intent-to-treat population overall and in post hoc subgroups of participants with any pruritus at baseline (daily average ItchRO > 0) and those with daily average ItchRO ≥ 3 at baseline. (B) Mean change in ItchRO weekly sum score from baseline at all assessment time points. Error bars represent 95% CIs. (C) Mean change in 5-D Itch score from baseline to week 14/ET in the modified intent-to-treat population overall and in post hoc subgroups of participants with any pruritus at baseline (daily average ItchRO > 0) and those with daily average ItchRO ≥ 3 at baseline. (D) Mean change in 5-D Itch score from baseline at all assessment time points. Error bars represent 95% CIs. *p*-values are from paired Wilcoxon signed-rank tests. Abbreviations: 5-D Itch, 5-domain Itch; BL, baseline; ET, early termination; ItchRO, Itch-Reported Outcome; NS, no significance.

surprisingly, 7αC4 levels, a marker of BA synthesis, increased by 252.9% ($p < 0.0001$). In addition, mean FGF-19 levels decreased by 19.6% ($p = 0.0005$), mean total cholesterol decreased by 10.1% ($p = 0.0002$), and mean LDL-C decreased by 12.8% ($p < 0.0001$). Significant changes in most of these biomarkers were also observed from baseline to week 6 (Table 5).

Levels of ALT, AST, ALP, and total bilirubin did not significantly change from baseline to week 14/ET (Table 5). The 34.6% mean increase in conjugated

TABLE 3 Pruritus, health-related quality of life, and sleep outcomes

	mITT Population (N = 27)		
Variable	**Baseline**	**Change to week 6**	**Change to week 14/ET**
Pruritus			
5-D Itch score[a]	11.8 (9.7, 13.9)	–3.5 (–5.7, –1.2)[b,c]	–3.8 (–5.9, –1.7)[d]
HRQoL and sleep			
PBC-40 Fatigue[e]	22.15 (18.29, 26.01)	+0.00 (–2.53, 2.53)	+0.54 (–2.04, 3.11)
MOS-Sleep Disturbance[f]	31.48 (20.33, 42.63)	–5.05 (–13.98, 3.88)[b]	–6.44 (–15.35, 2.48)

All values are mean (95% CI).
[a]5-D Itch was scored from 5 (no pruritus) to 25 (most severe).
[b]Data were missing in 1 patient.
[c]$p < 0.01$ (Wilcoxon signed-rank test).
[d]$p < 0.0001$ (Wilcoxon signed-rank test).
[e]PBC-40 Fatigue domain was scored from 11 to 55; lower scores represent better HRQoL.
[f]The MOS-Sleep questionnaire evaluated 12 parameters across 6 dimensions. The sleep disturbance dimension included "trouble falling asleep," "sleep restlessness," "awaken during sleep," and "time to fall asleep," and was scored from 0 to 100; higher scores indicate greater sleep dysfunction.
Abbreviations: 5-D Itch, 5-domain Itch; ET, early termination; HRQoL, health-related quality of life; mITT, modified intent-to-treat; MOS-Sleep, Medical Outcomes Study Sleep; PBC-40, primary biliary cholangitis-specific HRQoL questionnaire.

TABLE 4 Serum bile acids over time

Variable (μmol/L)	Time point	ItchRO ≥ 3 (n = 8)	CFB, %	sBA > 10 (n = 18)	CFB, %	All (N = 27)	CFB, %
sBA	Baseline	73.13 (43.02, 103.24)	—	55.58 (36.95, 74.21)	—	38.94 (23.65, 54.24)	—
	Week 6	33.52 (2.27, 64.76)	−39.61 (−75.36, −3.86)[a]	22.03 (8.32, 35.74)	− 33.55 (−50.70, −16.41)[c]	16.50 (7.10, 25.91)	−22.44 (−35.19, −9.69)[d]
	Week 14/ET	41.07 (2.29, 79.85)	−32.06 (−75.00, 10.89)	33.24 (14.95, 51.53)	−22.34 (−40.38, −4.30)[b]	24.10 (11.21, 36.99)	−14.84 (−27.25, −2.43)[b]
GCA	Baseline	22.82 (11.01, 34.62)	—	14.73 (8.57, 20.89)	—	10.24 (5.52, 14.97)	—
	Week 6	9.77 (−1.78, 21.33)	−13.04 (−25.50, −0.58)[a]	5.76 (0.79, 10.73)	−8.97 (−14.37, −3.57)[c]	4.15 (0.81, 7.48)	−6.10 (−9.95, −2.25)[d]
	Week 14/ET	12.11 (−1.82, 26.04)	−10.71 (−24.56, 3.15)	8.58 (2.50, 14.66)	−6.15 (−12.15, −0.16)[a]	6.01 (1.83, 10.19)	−4.24 (−8.25, −0.22)[a]
TCA, μmol/L	Baseline	15.55 (9.66, 21.44)	—	12.19 (6.72, 17.66)	—	8.40 (4.27, 12.53)	—
	Week 6	3.23 (−0.20, 6.65)	−12.32 (−19.14, −5.50)[b]	2.24 (0.69, 3.78)	−9.95 (−14.93, −4.97)[d]	1.56 (0.50, 2.63)	−6.84 (−10.50, −3.18)[d]
	Week 14/ET	4.57 (−0.30, 9.44)	−10.98 (−18.64, −3.32)[a]	4.59 (0.72, 8.47)	−7.59 (−11.57, −3.62)[d]	3.13 (0.50, 5.75)	−5.28 (−8.16, −2.39)[d]
TCDCA	Baseline	9.29 (6.11, 12.46)	—	8.58 (4.31, 12.85)	—	5.89 (2.74, 9.04)	—
	Week 6	3.08 (0.83, 5.33)	−6.21 (−10.33, −2.08)[a]	2.53 (1.16, 3.90)	−6.05 (−9.55, −2.55)[c]	1.77 (0.78, 2.75)	−4.12 (−6.63, −1.62)[d]
	Week 14/ET	4.10 (0.39, 7.81)	−5.19 (−10.53, 0.15)	4.25 (1.26, 7.23)	−4.33 (−7.00, −1.66)[c]	2.92 (0.86, 4.99)	−2.97 (−4.85, −1.08)[d]
GCDCA	Baseline	22.74 (11.19, 34.30)	—	16.74 (10.91, 22.56)	—	11.68 (6.95, 16.41)	—
	Week 6	14.34 (2.81, 25.87)	−8.40 (−20.34, 3.54)	9.06 (3.78, 14.34)	−7.68 (−12.71, −2.64)[b]	6.63 (2.95, 10.30)	−5.05 (−8.63, −1.48)[b]
	Week 14/ET	17.44 (2.99, 31.89)	−5.30 (−20.52, 9.92)	13.01 (6.35, 19.67)	−3.72 (−10.08, 2.64)	9.59 (4.86, 14.33)	−2.09 (−6.31, 2.14)

Note: All values are mean (95% CI).
[a]p <0.05 (Wilcoxon signed-rank test).
[b]p < 0.01 (Wilcoxon signed-rank test).
[c]p < 0.001 (Wilcoxon signed-rank test).
[d]p < 0.0001 (Wilcoxon signed-rank test).
Abbreviations: CFB, change from baseline; ET, early termination; GCA, glycocholic acid; GCDCA, glycochenodeoxycholic acid; ItchRO, Itch-Reported Outcome; sBA, serum bile acid; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid.

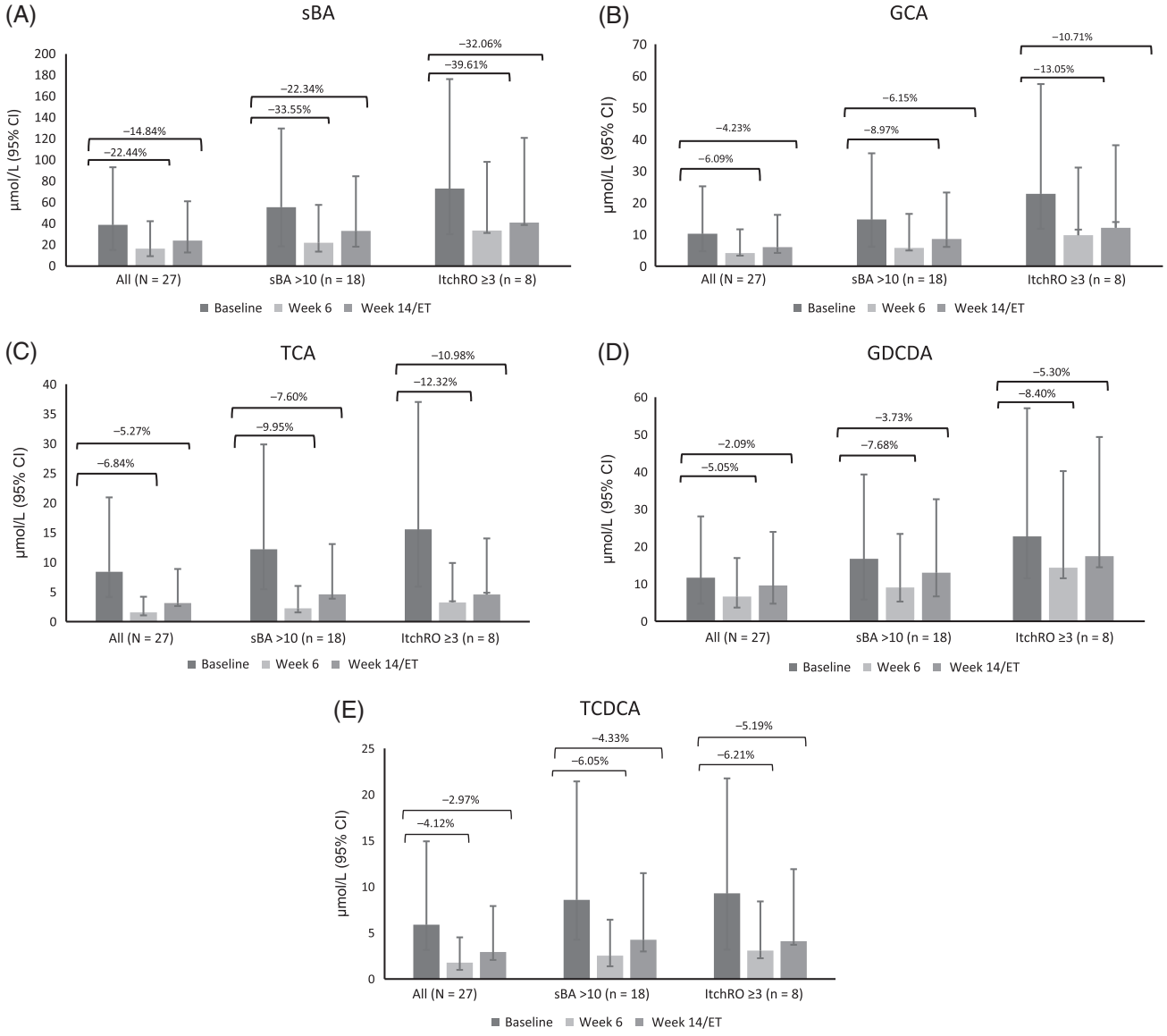

FIGURE 2 Serum bile acids over time. Mean change in sBA, and conjugated BA subspecies levels from baseline through to week 6 and week 14/ET in all participants (N = 27), participants with ItchRO score ≥ 3 (n = 8), and participants with sBA levels > 10. (A) sBA (µmol/L); (B) GCA (µmol/L); (C) TCA (µmol/L); (D) GCDCA (µmol/L); (E) TCDCA (µmol/L). Mean values are presented; error bars represent 95% CI; percentages represent change from baseline. Abbreviations: BA, bile acid; CFB, change from baseline; ET, early termination; GCA, glycocholic acid; GCDCA, glycochenodeoxycholic acid; ItchRO, Itch-Reported Outcome; sBA, serum bile acid; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid.

bilirubin levels was statistically significant at week 14/ET ($p = 0.0462$), from a mean baseline value of 0.60 mg/dL (95% CI, 0.40–0.81), but was of unknown clinical significance.

DISCUSSION

This open-label study was the first to assess the safety and efficacy of a selective IBAT inhibitor in adults with PSC. Pruritus scores and sBA concentrations significantly decreased over 14 weeks of maralixibat treatment, even though the patient population for this study was not required to have a prespecified itch severity. Baseline sBA levels were positively correlated with baseline ItchRO scores, and an improvement in itch of 12.6% was seen in the overall population; improvement in pruritus was 70% in a subgroup of 8 participants with daily average ItchRO scores of 3/10 or higher at baseline. These results strongly support the potential efficacy of sBA reduction by IBAT inhibition with maralixibat for the treatment of pruritus associated with PSC. Although there was no correlation between ALP and ItchRO weekly sum scores at baseline, a negative correlation between these 2 parameters was seen at week 14/ET for the overall patient population (N = 27) and ItchRO daily score > 0 subpopulation (n = 18). Further analysis of these

TABLE 5 Biomarkers and laboratory parameters

Variable	mITT population (N = 27)		
	Baseline	Change to week 6	Change to week 14/ET
Biomarkers of cholestasis			
sBA, μmol/L	38.94 (23.65, 54.24)	−22.44 (−35.19, −9.69)[a]	−14.84 (−27.25, −2.43)[b]
Total cholesterol, mg/dL	213.0 (193.0, 233.1)	−19.5 (−28.1, −10.8)[a]	−21.2 (−31.3, −11.1)[c]
LDL-C, mg/dL	121.4 (105.4, 137.5)	−14.9 (−22.3, −7.6)[c]	−16.3 (−23.3, −9.3)[a]
Biomarkers of BA synthesis			
7αC4, ng/mL	8.53 (4.61, 12.44)	+9.05 (2.44, 15.66)[c]	+11.09 (5.71, 16.47)[a]
Autotaxin, ng/mL	578.83 (394.14, 763.52)	−65.15 (−194.98, 64.68)	−148.39 (−274.70, −22.07)[c]
FGF-19, pg/mL	183.54 (111.23, 255.85)	−71.73 (−142.12, −1.33)[b]	−65.75 (−106.22, −25.28)[c]
FGF-21, pg/mL	146.04 (83.91, 208.17)	+55.43 (−17.13, 127.98)	+82.91 (−48.96, 214.77)
Liver chemistry			
ALP, U/L[d]	471.6 (346.2, 596.9)	+18.0 (−23.1, 59.1)	+36.7 (−30.9, 104.3)
ALT, U/L[d]	108.5 (77.2, 139.7)	+4.3 (−16.3, 24.9)	+10.5 (−14.5, 35.4)
AST, U/L[d]	88.3 (71.0, 105.6)	+5.0 (−5.3, 15.3)	+11.7 (−1.8, 25.2)
Total bilirubin, mg/dL[d]	1.22 (0.91, 1.52)	−0.01 (−0.17, 0.15)	+0.24 (−0.02, 0.51)
Conjugated bilirubin, mg/dL[d]	0.60 (0.40, 0.81)	+0.02 (−0.07, 0.11)	+0.19 (0.01, 0.37)[e]

Note: All values are mean (95% CI).
[a]$p < 0.0001$ (paired *t* test or paired Wilcoxon signed-rank test).
[b]$p < 0.01$.
[c]$p < 0.001$
[d]ALP, ALT, AST, and bilirubin were also assessed at week 3.
[e]$p < 0.05$.
Abbreviations: 7αC4, 7α-hydroxy-4-cholesten-3-one; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BA, bile acid; ET, early termination; LDL-C, LDL-cholesterol; mITT, modified intent-to-treat; sBA, serum bile acid.

results is warranted to explore whether the course of change in ALP levels can predict the severity of pruritus, or *vice versa*.

Maralixibat was generally well tolerated, and no unexpected safety signals were observed, consistent with previous studies of IBAT inhibitors.[8,16–18] Gastrointestinal TEAEs were reported in most participants, and diarrhea was the most common TEAE (affecting 51.9% of participants). Gastrointestinal TEAEs and diarrhea in participants taking IBAT inhibitors are an expected result of increased concentrations of BAs in the colon.[11,16] BAs increase mucosal permeability by activating intracellular secretory processes, resulting in additional mucus secretion and inhibition of chloride hydroxyl exchange.[34] Increases in the severity of gastrointestinal signs and symptoms were moderate in the present study, according to self-rated participant scores, and 1 participant withdrew from the study due to a gastrointestinal TEAE. Furthermore, the incidence of gastrointestinal TEAEs appeared to attenuate over time both in this study and in a previous study of maralixibat in adults with PBC.[18] In prior clinical trials of maralixibat for Alagille syndrome and PFIC, treatment interruptions or dose reductions occurred in ~6% of patients due to gastrointestinal events, compared with 18.5% in the current study.[35,36] Nevertheless, maralixibat was generally well tolerated in this PSC population of participants with a high prevalence of IBD, who might be expected to experience greater gastrointestinal AEs.

As expected, sBA levels decreased over the course of the study, by 16.7% from baseline to week 14/ET in participants overall and by 40.0% in those participants whose sBA was elevated above normal at baseline. This finding reflects the mechanism of action of maralixibat and is consistent with reduced reabsorption of BAs following IBAT inhibition. Consistent with previous studies, the reduction in sBA levels was accompanied by an increase in serum 7αC4 levels, indicating compensatory upregulation in *de novo* BA production following BA depletion.[11,37] The decreased levels of serum cholesterol reported in this study are also consistent with increased BA synthesis associated with IBAT inhibition by maralixibat.

The severity of pruritus was reduced consistently during maralixibat treatment across all measures used in this study (ItchRO, 5-D Itch, and Patient Impression of Change). Improvements in pruritus with IBAT inhibitors have been reported previously in patients with Alagille syndrome[20,38] and PFIC.[19,21] Although the broad peroxisome proliferator-activated receptor agonist bezafibrate has shown efficacy in the treatment of severe pruritus in PSC, it is not currently approved for use in the US.[39] To the authors' knowledge, the present study provides the first evidence that treatment with an IBAT inhibitor is associated with reduced

pruritus in patients with PSC. Most participants (69.2%) reported that the reductions in pruritus outweighed the adverse effects of maralixibat treatment, but this was not reflected in significant improvements in sleep. It is possible that the beneficial effects on pruritus may have been tempered by other factors, such as gastrointestinal adverse effects, particularly in participants with a history of UC/IBD. IBAT inhibitors may be most effective at reducing itching in patients with severe and debilitating pruritus but without associated IBD, such as those with Alagille syndrome and PFIC, since the underlying burden of gastrointestinal-related AEs, including nausea and abdominal pain, tends to be relatively low in these diseases.[10,21,40]

Accumulation of BAs in the liver causes hepatotoxicity and can increase the risk of inflammation and liver cancer.[7] Higher baseline levels of total sBA and conjugated primary BAs, including glycocholic acid and TCA, have been shown to be associated with an increased risk of clinical disease progression in patients with PSC.[41–43] In the present study, baseline sBA levels were correlated with ItchRO scores and treatment with maralixibat was associated with significant decreases in total sBA levels and with levels of conjugated primary BAs (glycocholic acid, TCA, and taurochenodeoxycholic acid). This reduction in sBA levels and primary conjugated BAs suggests that maralixibat may have beneficial treatment effects beyond a reduction in itch. Glycochenodeoxycholic acid, another primary conjugated BA, did not show an associated significant decrease after treatment with maralixibat.

Preventing accumulation of cytotoxic BAs in the liver may be clinically useful because high BA levels are associated with an increased risk of clinical disease progression in patients with PSC.[41,42,44] Moreover, the accumulation of some BA subspecies, such as primary glycine and taurine conjugates and deoxycholic acid, have been associated with cell and DNA damage.[41,42,44,45] Levels of TCA are known to be increased in patients with cirrhosis and may directly promote liver damage through upregulation of toll-like receptor 4 and activation of hepatic stellate cells.[42,43] In addition, taurochenodeoxycholic acid and taurolithocholic acid have been long known to be hepatotoxic.[46,47]

Although preclinical studies have suggested a potential benefit of IBAT inhibition in PSC, no significant improvements in liver biochemistries were noted; however, the design and patient population for the present study were not selected to address this issue.[48] Liver function remained stable in patients with PSC during treatment with maralixibat at the doses studied with no evidence of hepatoxicity. The clinical significance of the increase in conjugated bilirubin levels during the study is not clear. Changes in levels of other liver function biomarkers (ALT, AST, and ALP) and total bilirubin were not significant. Whether these represent natural fluctuations in patients with PSC is unclear; notably, there was no requirement in this study for participants to have prespecified or stable ALP levels at entry, whereas recent trials now require stability with <30% ALP fluctuation during screening assessment.[49]

The limitations of this pilot study include the lack of a placebo control, the small study population, and the limited duration. The key strength is the exposure of a minimum number of participants to an investigational new drug to gain sufficient evidence to guide future clinical development. Comorbid IBD in a substantial majority of patients is a feature of PSC and may have confounded assessment of gastrointestinal TEAEs and the tolerability of maralixibat. The maximum maralixibat dose in this study was 10 mg/d to limit gastrointestinal adverse effects, but some participants might have been able to tolerate higher doses, limiting the ability to assess the full effect of maralixibat in PSC, which has been shown in previous studies in PFIC where doses of up to 560 μg/kg/d were administered with no increase in TEAEs compared with lower doses.[21] However, since this is the first study of IBAT inhibitors in PSC, it was important to ensure the safety of all participants. In addition, as there were no patient selection criteria relating to pruritus and sBA levels, the ability to detect improvements in pruritus may have been limited.

In conclusion, the reductions in sBA levels and accompanying improvement in pruritus, together with the tolerable gastrointestinal TEAEs, are consistent with the expected mechanism of action of maralixibat. Given these effects are not accompanied by deterioration of the liver in this study, or in other phase 2 studies in patients with Alagille syndrome and PBC,[17,18,20] the findings of the present study further support clinical investigation of maralixibat or other IBAT inhibitors as treatments for pruritus in adults with PSC.

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CONFLICTS OF INTEREST

Christopher L. Bowlus has received payments through their institution from Mirum Pharmaceuticals, Inc.; received grants from CymaBay, BMS, GSK, Intercept, Hanmi, TARGET, Pliant, Eli Lilly, GENFIT, Novartis, Takeda, Arena Pharmaceuticals, and Calliditas; and served as a consultant for CymaBay, GSK, Eli Lilly, Shire, and Mirum Pharmaceuticals Inc. Cynthia A. Moylan has received research grants from Exact Sciences and GSK. Paul J. Pockros has served as an advisor for Intercept, Gilead, and AbbVie; served as a speaker for Intercept; received research grants from Intercept; and received unrestricted grants from Gilead and AbbVie. Alejandro Dorenbaum was a prior stock owner (fully divested) of Mirum Pharmaceuticals Inc. Ciara Kennedy is a stock holder and company founder of Mirum Pharmaceuticals Inc. Thomas Jaecklin owns stocks and has intellectual property rights in Mirum Pharmaceuticals Inc. and owns stocks in and is employed by Galapagos. Andrew McKibben owns stocks in and is employed by Mirum Pharmaceuticals Inc. Elaine Chien owns stocks in and is employed by Mirum Pharmaceuticals Inc. Marshall Baek owns stocks in and is employed by Mirum Pharmaceuticals Inc. Pamela Vig owns stocks in and is employed by Mirum Pharmaceuticals Inc. Cynthia Levy has received research grants through their institution from Calliditas, Cara Therapeutics, CymaBay, GENFIT, Gilead, GSK, Intercept, Novartis, HighTide, Zydus, Mirum Pharmaceuticals Inc., Escient, Pliant, and Target PharmaSolutions; has served as a consultant for CymaBay, GENFIT, DISC, GSK, Ipsen, Pliant, Mirum Pharmaceuticals Inc., Calliditas, and Intercept; serves as associate editor for *Hepatology*; and is a member of the ABIM Test and Policy committee for Transplant Hepatology. The remaining authors have no conflicts to report.

DATA AVAILABILITY STATEMENT

Beginning 6 months and ending 5 years after publication, de-identified participant data from the clinical trial might be made available to investigators whose proposed use of the data has been approved by a review committee, including the primary authors as the study funder. The study protocol will also be available via weblink. Proposals should be directed to medinfo@mirumpharma.com. Before being granted access, data requesters will be required to sign a data access agreement.

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